I. Priority claim

The Examiner requested that the "specification on page 1 should be amended to reflect the claim to domestic priority under 35 USC 119(e), serial numbers 60/099,471 and 60/112,855." (Office Action, page 2.) The specification is amended above as requested by the Examiner.

II. Rejection of claims 14 to 16 under 35 U.S.C 112, second paragraph

The Examiner rejected claims 14 to 16 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. In particular, the Examiner stated that claim 14 and its dependent claims were indefinite, as in order for one of skill in the art to practice the claimed invention, "the claim must include a resolution step." (Office Action, page 2, paragraph 5.)

Claim 14 is amended above to include a resolution step as requested by the Examiner. Amended claim 14 is thus clear and definite, as are claims 15 and 16, which depend directly from claim 14. As claims 14 to 16 are clear and definite, rejection of claims 14 to 16 is overcome. Therefore, Applicants respectfully request that the rejection of claims 14 to 16 under 35 U.S.C. 112, second paragraph, be withdrawn.

III. Rejection under 35 U.S.C. 102(b)

The Examiner rejected claims 14 and 15 under 35 U.S.C 102(b) as being anticipated by WO 96/38172. The Examiner stated that " [t]he '172 patent teaches a method of detecting kidney fibrosis (i.e. a disease caused by overproduction of extracellular matrix) by detecting CTGF and comparing said detection to a standard (page 3 and 7, in particular)." (Office Action, page 3.) The rejection of claims 14 and 15 under 35 U.S.C. 102(b) as being anticipated by WO 96/38172 is respectfully traversed.

WO 96/38172 relates to methods of diagnosing pathologies characterized by a cell proliferative disorder. Specifically, WO 96/38172 provides a "method of diagnosing pathological states in a subject suspected of having pathology characterized by a cell proliferative disorder..." (WO 96/38172, page 3, lines 23 to 25.) WO 96/38172 describes cell proliferative disorders as

"pathological states characterized by the continual multiplication of cells resulting in an overgrowth of a cell population...(end of sentence)." (WO 96/38172, page 15, lines 29 to 30.)

Claim 14 of the instant application is directed to a method of diagnosing "a renal disorder characterized by overproduction of extracellular matrix" in a subject by measuring the levels of CTGF in a sample from the subject. WO 96/38172 does not disclose a renal disorder "characterized by overproduction of extracellular matrix" as recited in the instant claims. Therefore, WO 96/38172 does not anticipate these claims. As WO 96/38172 does not anticipate claims 14 and 15, withdrawal of the rejection of these claims as being anticipated by this reference under 35 U.S.C. 102(b) is respectfully requested.

IV. Rejection under 35 U.S.C. 102 (a)

The Examiner rejected claims 14 and 15 under 35 U.S.C. 102(a) as being anticipated by Ito et al. The rejection of claims 14 and 15 under 35 U.S.C. 102(a) as anticipated by Ito et al. is respectfully traversed.

The Examiner stated "Ito et al., teaches a method of detecting kidney fibrosis (i.e. a disease caused by overproduction of extracellular matrix) in diabetic patients by detecting CTGF and comparing said detection to a standard (Figure 5 and Table 1 in particular)." (Office Action, page 3.)

Ito investigated the involvement of CTGF in renal fibrosis by examining CTGF mRNA expression in human biopsy specimens. Figure 5 of this publication, cited by the Examiner, shows *in situ* hybridization analysis of CTGF mRNA expression in proliferative lesions in diabetes mellitus and IgA nephropathy. Table 1 of this publication, also cited by the Examiner, presents a list of renal biopsy cases evaluated for CTGF mRNA expression. Ito, therefore, provides methods of detecting CTGF mRNA in biopsied tissue samples. As known in the art, an increase in mRNA levels does not necessarily correspond to an increase in protein levels.

Claim 14 of the present application is directed to a method of diagnosing a renal disorder characterized by overproduction of extracellular matrix in a subject by "detecting the level of

CTGF" in a sample from the subject. As noted in the present specification, Ito "did not include quantitative results or any measurement of CTGF protein levels." (Page 7, line 24 of the present application.) Therefore, Ito does not anticipate claims 14 and 15. Withdrawal of the rejection of claims 14 and 15 as being anticipated under 35 U.S.C. 102(a) by this reference is thus respectfully requested.

V. Rejections under 35 U.S.C. 103

The Examiner rejected claim 17 under 35 U.S.C. 103 as being unpatentable over Ito et al. or WO 96/38172. The Examiner stated "it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to assay for the presence of CTGF to detect kidney fibrosis as taught by Ito et al., or WO 96/38172, and package the assay as a kit with the expectation that kits allow for ease and commercial reproducibility of known assays." (Office Action, page 4.) The rejection of claim 17 under 35 U.S.C. 103 as being unpatentable over Ito et al. or WO 96/38172 is respectfully traversed.

The Examiner stated that the claimed invention differs from prior art teaching(s) only by recitation of a kit. (See Office Action, page 4.) Claim 17 is directed to "[a] diagnostic kit for use in diagnosing a renal disorder characterized by overproduction of extracellular matrix, or identifying a predisposition or susceptibility to a renal disorder characterized by overproduction of extracellular matrix." As discussed above, Ito investigated CTGF mRNA expression in human biopsy specimens using *in situ* hybridization. Ito contains no teaching or suggestion of diagnosing a renal disorder using direct measurement of CTGF protein levels in patient samples as in the present invention.

Furthermore, Applicants note that the present invention is directed to methods of diagnosing a renal disorder characterized by overproduction of extracellular matrix by detecting levels of CTGF. In particular, Applicants are the first to demonstrate the production of CTGF protein in renal cells. The present invention provides the first demonstration that extracellular matrix overproduction in mesangial cells is related to CTGF. Specifically, Applicants showed that mesangial cells produce and secrete CTGF protein. (See Example 2, and Figures 4A and 4B.)

Applicants further established that CTGF increased extracellular matrix production in these cells. Specifically, CTGF stimulated the production of fibronectin and collagen type I by mesangial cells. (See, Example 1, Figures 1A and 1B.) The present invention thus provides support for the role of CTGF in the pathogenesis of renal disorders by demonstrating that CTGF stimulates mesangial cells to produce, deposit, and accumulate extracellular matrix components. Therefore, the present invention provides the first demonstration that extracellular matrix overproduction in mesangial cells is directly related to CTGF.

Ito investigated CTGF mRNA expression in human biopsy specimens of various renal diseases. Ito does not disclose a method for detecting CTGF as a method of diagnosing a renal disorder. Additionally, Ito contains no teaching or suggestion of a diagnostic kit useful for detecting the level of CTGF as a method of diagnosing a renal disorder. Therefore, Ito does not in any way teach or suggest the diagnostic kit of claim 17, and claim 17 is thus patentable over Ito.

WO 96/38172 fails to cure the deficiencies of Ito. The Examiner cited WO 96/38172 as teaching "a method of detecting kidney fibrosis." Applicants note that, as discussed above, the present invention is directed to methods of diagnosing a renal disorder "characterized by overproduction of extracellular matrix." WO 96/38172 relates to methods of diagnosing pathologies characterized by a cell proliferative disorder. As noted above with respect to Ito, WO 96/38172 fails to teach or suggest a method of diagnosing a renal disorder characterized by overproduction of extracellular matrix as recited in the instant claims. Additionally, WO 96/38172 contains no teaching or suggestion of a diagnostic kit for diagnosing a renal disorder characterized by overproduction of extracellular matrix. Therefore, WO 96/38172 does not teach or suggest the diagnostic kit of claim 17, and claim 17 is thus patentable over WO 96/38172.

Neither Ito nor WO 96/38172 teach or suggest the diagnostic kit of claim 17, nor do they provide any motivation for deriving the claimed kit. Claim 17 is thus patentable over both of these references, singly or in combination. Withdrawal of the rejection of claim 17 as being unpatentable over these references under 35 U.S.C. 103 is thus respectfully requested.

CONCLUSION

Applicants believe all claims are allowable in view of the above remarks. The Examiner's indication that claim 18 is allowable is appreciated.

If there are any questions regarding the communication or the above-referenced application, please call Applicant's Attorney at 650-866-7254.

Respectfully submitted,

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Leanne C. Price, Esq.
Reg. No. 42,090

FibroGen, Inc.
225 Gateway Boulevard
South San Francisco, CA 94080
Main: 650-866-7200
Direct: 650-866-7254
Facsimile: 650-866-7292